UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/514,427	11/16/2004	Sui Xiong Cai	1735.0770001/RWE/CJW	4080

26111 7590 05/15/2007

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
O DELL, DAVID K	

ART UNIT	PAPER NUMBER
1609	

MAIL DATE	DELIVERY MODE
05/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/514,427	CAI ET AL.	
	Examiner	Art Unit	
	David K. O'Dell, Ph.D.	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-92* is/are pending in the application.

4a) Of the above claim(s) *41-53,55, 56 and 65-92* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-40,54 and 57-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. ____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 November 2006, 12 June 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-92 are pending in the current application.

2. This is a National Stage of PCT/US03/15427, filed May 16, 2003, which claims priority to U.S. Provisional Application No. 60/378,079, filed May 16, 2002.

Response to Restriction Election

3. Applicant's election with traverse of Group I in the reply filed on March 11, 2007 is acknowledged. The traversal is on the ground(s) that "Applicants respectfully disagree. The substructure search on page 9 of the Office Action does not represent Applicant's "compound core." The substructure constructed by the Examiner contains just 2 rings and a pendant nitrogen atom which may or may not be part of a fused ring system. This substructure search indicates a large number of projected answers. In contrast, claim 1 requires there to be a tricyclic ring system core containing the nitrogen atom. In the attached substructure search (Exhibit A) of the tricyclic ring system containing a pyrrolo ring, 4 published documents were obtained.~ Each of these published documents have inventors common with the inventors of the present application. See also the attached search output (Exhibit B) which gives the registry numbers of the compounds which match the structure of the substructure search. In view of the inventive common core, Applicants respectfully request rejoinder of at least Groups II-VI together with Group I." This is found persuasive because applicant has redefined what is considered the core, and provided evidence for the novelty of this core. Since this was not the core submitted to the examiner (previously A was represented by a plethora of possible permuations not limited to 5 membered mono-

nitrogen heterocycles as described in Exhibits A and B), and the applicant has redefined the core the examiner hereby rejoins Groups II-XII with Group I.

Group I, Claims 1-9, 11-19, 21-23, 54, 57-64 drawn to compounds and compositions possessing a phenyl-pyrrolo[2,3-*h*]chromene core where in applicant's Markush structure Formula I A is phenyl, D is fused pyrrole, Y=CN, Z=NH_2, or $NR_{22}R_{23}$ R_3=R_4=R_5=R_{22}=R_{23}=H shown as structure **I** in Figure 1, with the proviso that no compositions contain currently marketed pharmaceuticals. Claims 1-8, 10-20, 24-26, 54, 57-64 drawn to compounds and compositions possessing a 3-pyridyl-pyrrolo[2,3-*h*]chromene core where in applicant's Markush structure Formula I A is 3-pyridyl, D is fused pyrrole, Y=CN, Z=NH_2, or $NR_{22}R_{23}$ R_3=R_4=R_5=R_{22}=R_{23}=H shown as structure **II** in Figure 1, with the proviso that no compositions contain currently marketed pharmaceuticals. Claims 1-8, 10-20, 24-26, 54, 57-64 drawn to compounds and compositions possessing a 2-quinoxalinyl-pyrrolo[2,3-*h*]chromene core where in applicant's Markush structure Formula I A is 2-quinoxalinyl, D is fused pyrrole, Y=CN, Z=NH_2, or $NR_{22}R_{23}$ R_3=R_4=R_5=R_{22}=R_{23}=H shown as structure **III** in Figure 1, with the proviso that no compositions contain currently marketed pharmaceuticals. Claims 1-8, 11-20, 54, 57-64 drawn to compounds and compositions possessing a 2-pyrazinyl-pyrrolo[2,3-*h*]chromene core where in applicant's Markush structure Formula I A is 2-pyrazinyl, D is fused pyrrole, Y=CN, Z=NH_2, or $NR_{22}R_{23}$ R_3=R_4=R_5=R_{22}=R_{23}=H shown as structure **IV** in Figure 1, with the proviso that no compositions contain currently marketed pharmaceuticals. Claims 1-8, 11-19, 54, 57-64 drawn to compounds and compositions possessing a 2-thiophenyl-pyrrolo[2,3-*h*]chromene core where in applicant's Markush structure Formula I A is 2-thiophenyl, D is fused pyrrole, Y=CN, Z=NH_2, or $NR_{22}R_{23}$ R_3=R_4=R_5=R_{22}=R_{23}=H shown as structure **V** in Figure 1, with the proviso that no compositions contain currently marketed pharmaceuticals. Claims 1-8, 11-19, 54, 57-64 drawn to compounds and compositions possessing a 3-indolyl-pyrrolo[2,3-*h*]chromene core where in applicant's Markush structure Formula I A is 3-indolyl, D is fused pyrrole, Y=CN, Z=NH_2, or $NR_{22}R_{23}$ R_3=R_4=R_5=R_{22}=R_{23}=H shown as structure **VI** in Figure 1, with the proviso that no compositions contain currently marketed pharmaceuticals. Claims 1-8, 11-19, 54, 57-64 drawn to compounds and compositions possessing a 3-indolyl-pyrrolo[2,3-*h*]chromene core where in applicant's Markush structure Formula I A is 3-indolyl, D is fused pyrrole, Y=CN, Z=NH_2, or $NR_{22}R_{23}$ R_3=R_4=R_5=R_{22}=R_{23}=H shown as structure **VI** in Figure 1, with the proviso that no compositions contain currently marketed pharmaceuticals. Claims 1-9, 11, 27-37, 54, 57-64 drawn to compounds and compositions possessing a phenyl-dihydropyrrolo[2,3-*h*]chromene core where in applicant's Markush structure Formula I A is phenyl, D is fused dihydropyrrole, Y=CN, Z=NH_2, or $NR_{22}R_{23}$ R_3=R_4=R_5=R_{22}=R_{23}=H shown as structure **VII** in Figure 1, with the proviso that no compositions contain currently marketed pharmaceuticals. Claims 1-8, 10, 11, 27-34, 38-40, 54, 57-64 drawn to compounds and compositions possessing a 3-pyridyl-dihydropyrrolo[2,3-*h*]chromene core where in applicant's Markush structure Formula I A is 3-pyridyl, D is fused

dihydropyrrole, Y=CN, Z=NH_2, or $NR_{22}R_{23}$ R_3=R_4=R_5=R_{22}=R_{23}=H shown as structure **VIII** in Figure 1, with the proviso that no compositions contain currently marketed pharmaceuticals. Claims 1-8, 11, 27-34, 54, 57-63 drawn to compounds and compositions possessing a 2-quinoxalinyl-dihydropyrrolo[2,3-*h*]chromene core where in applicant's Markush structure Formula I A is 2-quinoxalinyl, D is fused dihydropyrrole, Y=CN, Z=NH_2, or $NR_{22}R_{23}$ R_3=R_4=R_5=R_{22}=R_{23}=H shown as structure **IX** in Figure 1, with the proviso that no compositions contain currently marketed pharmaceuticals. Claims 1-8, 11, 27-34, 54, 57-63 drawn to compounds and compositions possessing a 2-pyrazinyl-dihydropyrrolo[2,3-*h*]chromene core where in applicant's Markush structure Formula I A is 2-pyrazinyl, D is fused dihydropyrrole, Y=CN, Z=NH_2, or $NR_{22}R_{23}$ R_3=R_4=R_5=R_{22}=R_{23}=H shown as structure **X** in Figure 1, with the proviso that no compositions contain currently marketed pharmaceuticals. Claims 1-8, 11, 27-34, 54, 57-63 drawn to compounds and compositions possessing a 2-thiophenyl-dihydropyrrolo[2,3-*h*]chromene core where in applicant's Markush structure Formula I A is 2-thiophenyl, D is fused dihydropyrrole, Y=CN, Z=NH_2, or $NR_{22}R_{23}$ R_3=R_4=R_5=R_{22}=R_{23}=H shown as structure **XI** in Figure 1, with the proviso that no compositions contain currently marketed pharmaceuticals. Claims 1-8, 11, 27-34, 54, 57-63 drawn to compounds and compositions possessing a 2-thiophenyl-dihydropyrrolo[2,3-*h*]chromene core where in applicant's Markush structure Formula I A is 2-thiophenyl, D is fused dihydropyrrole, Y=CN, Z=NH_2, or $NR_{22}R_{23}$ R_3=R_4=R_5=R_{22}=R_{23}=H shown as structure **XII** in Figure 1, with the proviso that no compositions contain currently marketed pharmaceuticals.

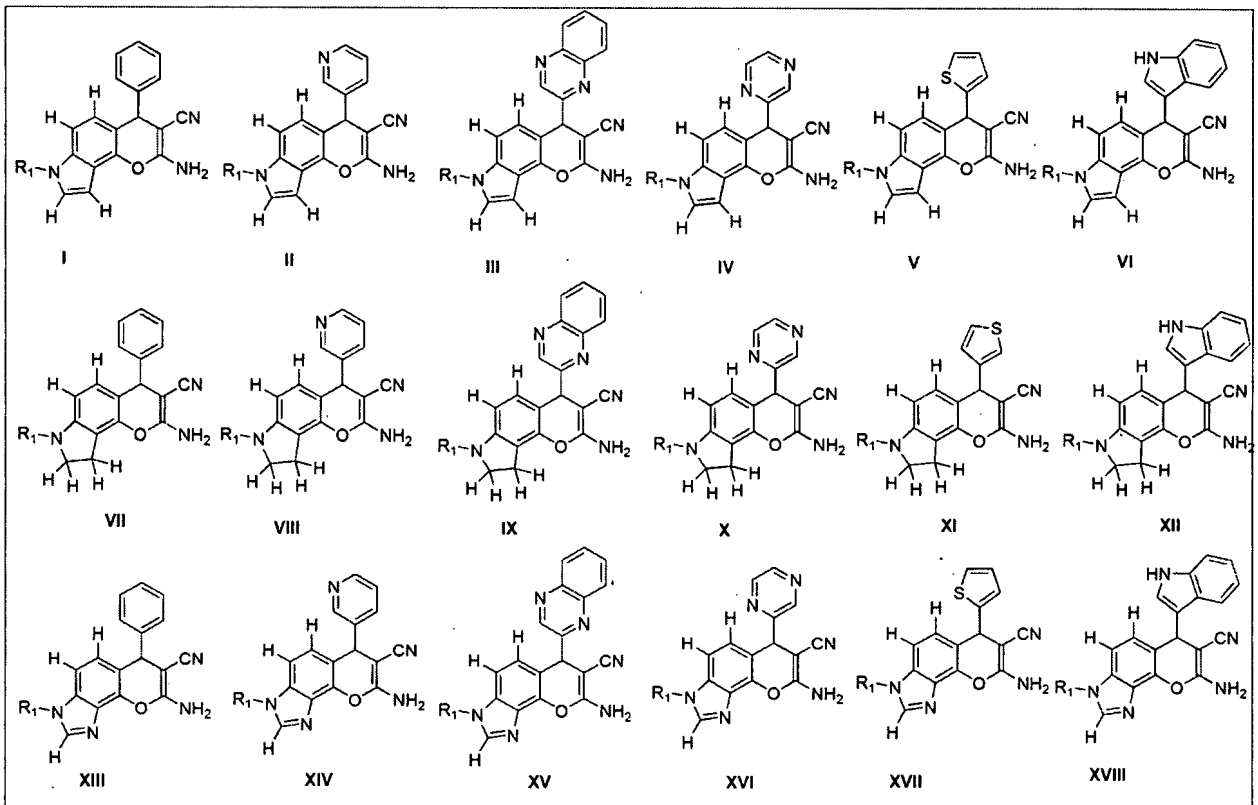


Figure 1. Groups I - XVIII

The requirement is deemed proper and is therefore made FINAL. Claims 1-40, 54, 57-64 are under examination.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

4. Claims 1-9, 11-19, 21-23, 54, 57-64 are rejected under 35 U.S.C. 102(a) as being anticipated by Drewe, J.A. et. al. WO 2001/034,591 (provided by applicant as FP13 on IDS). Drewe et. al. teaches number compounds of the instant case as shown below:

2-Amino-3-cyano-4-(3-methoxy-4,5-methylenedioxyphenyl)-4*H*-indolo[4,5-b]pyran;

2-Amino-3-cyano-4-(2-bromo-4,5-dimethoxyphenyl)-4*H*-indolo[4,5-b]pyran;

2-Amino-3-cyano-4-(3-bromo-4,5-dimethoxyphenyl)-4*H*-indolo[4,5-b]pyran;

2-Amino-3-cyano-4-(3-bromo-4,5-dimethoxyphenyl)-8-methyl-4*H*-indolo[4,5-b]pyran;

2-Amino-3-cyano-4-(3,4,5-trimethoxyphenyl)-4*H*-indolo[4,5-b]pyran;

2-Amino-3-cyano-4-(3-nitrophenyl)-4*H*-indolo[4,5-b]pyran;

2-Amino-3-cyano-4-(3-cyanophenyl)-4*H*-indolo[4,5-b]pyran;

2-Amino-3-cyano-7-dimethylamino-4-(3,5-difluorophenyl)-4*H*-chromene;

2-Amino-3-cyano-4-(3,5-dimethoxyphenyl)-4*H*-indolo[4,5-b]pyran;

Apparently these compounds are named as 4H-indolo[4,5b]pyrans as opposed to pyrollo[2,3h]chromenes (of the instant case), however these are in fact the same compounds.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-9, 11-19, 21-23, 54, 57-64 are provisionally rejected under 35 U.S.C. 102(e) as being anticipated by copending Application No. 11/150,586 (cited by applicant) which has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e), if published under 35 U.S.C. 122(b) or patented. This provisional rejection under 35 U.S.C. 102(e) is based upon a presumption of future publication or patenting of the copending application. The following compounds are contained within the application:

2-Amino-3-cyano-4-(3-methoxy-4,5-methylenedioxyphenyl)-4*H*-indolo[4,5-b]pyran;

2-Amino-3-cyano-4-(2-bromo-4,5-dimethoxyphenyl)-4*H*-indolo[4,5-b]pyran;

2-Amino-3-cyano-4-(3-bromo-4,5-dimethoxyphenyl)-4*H*-indolo[4,5-b]pyran;

2-Amino-3-cyano-4-(3-bromo-4,5-dimethoxyphenyl)-8-methyl-4*H*-indolo[4,5-b]pyran;

2-Amino-3-cyano-4-(3,4,5-trimethoxyphenyl)-4*H*-indolo[4,5-b]pyran;

2-Amino-3-cyano-4-(3-nitrophenyl)-4*H*-indolo[4,5-b]pyran;

2-Amino-3-cyano-4-(3-cyanophenyl)-4*H*-indolo[4,5-b]pyran;

2-Amino-3-cyano-4-(3,5-dimethoxyphenyl)-4*H*-indolo[4,5-b]pyran;

Apparently these compounds are named as 4H-indolo[4,5b]pyrans as opposed to pyrollo[2,3h]chromenes (of the instant case), however these are in fact the same compounds.

This provisional rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. This rejection may not be overcome by the filing of a terminal disclaimer. See *In re Bartfeld*, 925 F.2d 1450, 17 USPQ2d 1885 (Fed. Cir. 1991).

6. Claims 1-26, 54, 57-64 are provisionally rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent 7,053,117 B2 (cited by applicant as PG Pub 2003/0065018A) which has a common assignee with the instant application. The following compounds are contained within the patent:

EXAMPLE 36

2-Amino-3-cyano-4-(5-bromo-3-pyridyl)-4H-indolo [4,5-b]pyran

[0433] To a solution of 5-bromo-pyridine-3-carbaldehyde (94 mg, 0.505 mmol) and molanonitrile (34 mg, 0.505 mmol) in anhydrous ethanol (2.5 mL) was added 4-hydroxy-indole (70 mg, 0.526 mmol) and piperidine (0.1 mL, 1.0

and "2-Amino-3-cyano-4-(3,5-dichlorophenyl)-4H-indolo [4,5-b]pyran; 2-Amino-3-cyano-4-(3-chlorophenyl)-4H-indolo [4,5-b]pyran; 2-Amino-3-cyano-4-(3,5-difluorophenyl)-4H-indolo[4,5-b]pyran; 2-Amino-3-cyano-4-(3-fluorophenyl)-4H-indolo[4,5-b]pyran; 2 -Amino -3-cyano-4-(3 -pyridyl) -4H-indolo [4,5-b]pyran;2-Amino-3 -cyano -4-(5 -methyl- 3 -pyridyl) -4H-indolo [4,5-b]pyran;-2-Amino-3-cyano-4-(5-bromo-3-

pyridyl)-4H-indolo[4,5-b]pyran; 2-Amino-3-cyano-4-(5-methoxy-pyridin-3-yl)_4H_indolo[4,5_b]pyran; 2-Amino-3-cyano-4-(3-methoxyphenyl)-4H-indolo[4,5_b]pyran; 2-Amino-4-(3-bromo-4-hydroxy-5-methoxyphenyl)_3_cyano_4H_indolo[4,5-b]pyran; 2-Amino-3-cyano-4-(5-cyano-pyridin-3-yl)-4H_indolo[4,5_b]pyran; 2-Amino-3-cyano-4-(6-methylpyrazin.2_yl)_4H.indolo[4,5_b]pyran; 2-Amino-3-cyano-4-(quinoxalin-2-yl)-4H_indolo[4,5_b]pyran; 2-Amino-3-cyano-4-(3-bromo-4-phosphoric acid-di piperidine salt-5-methoxyphenyl)-4H-indolo[4,5-b]pyran; 2-Amino-3-cyano-4-phenyl- 1,4-dihydroquinoline; 2-Amino-3-ethoxycarboxyl-4-(3-bromo-4,5-dimethoxy-phenyl)-4H-indolo[4,5-b]pyran; 2-Amino-3-methylcarboxyl-4-(3-bromo-4,5-dimethoxy-phenyl)-4H-indolo[4,5-b]pyran; 2-Amino-4-(3-bromo-4,5-dimethoxyphenyl)-3-cyano-9-methyl-4H_ pyrrolo[3,2-h]chromene; 2-Amino-3-cyano-4-(3-pyridyl)-4H-indolo[4,5-b]pyran; ".....etc.

Apparently these compounds are named as both 4H-indolo[4,5b]pyrans and pyrollo[2,3h]chromenes in this document. The applied reference has a common assingee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

7. Claims 1-9, 11-19, 21-23, 54, 57-64 rejected under 35 U.S.C. 102(e) as being anticipated by Drewe, J.A. et. al. U.S. Patent 7,015,328 B2 (cited by applicant at

US29). The compounds mentioned in this action at 4. The applied reference has a common assingee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-40, 54, 57-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 48-51,54-81 of

copending Application No. 10/514,426. Although the conflicting claims are not identical, they are not patentably distinct from each other because they cover the same compounds and compositions.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

9. Claims 1-40, 54, 57-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17-9, 29, 30, 32, 61, 57 of copending Application No. 11/150,586. Although the conflicting claims are not identical, they are not patentably distinct from each other because they cover the same compounds and compositions.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

10. Claims 1-40, 54, 57-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 41-63, 73-78 of copending Application No. 11/072,499. Although the conflicting claims are not identical, they are not patentably distinct from each other because they cover the same compounds and compositions.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-40, 54, 57-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compound, does not reasonably provide enablement for the protracted list of substituents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing a variety of heterocycles, bearing multiple substitutions **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic chemist. **(C) The state of the prior art:** Little prior art exists on these complex compounds, however the synthesis will be evaluated on what is known using scientific principles. **(E) The level of predictability in the art:** Chemistry is unpredictable. See In Re Marzocchi and Horton

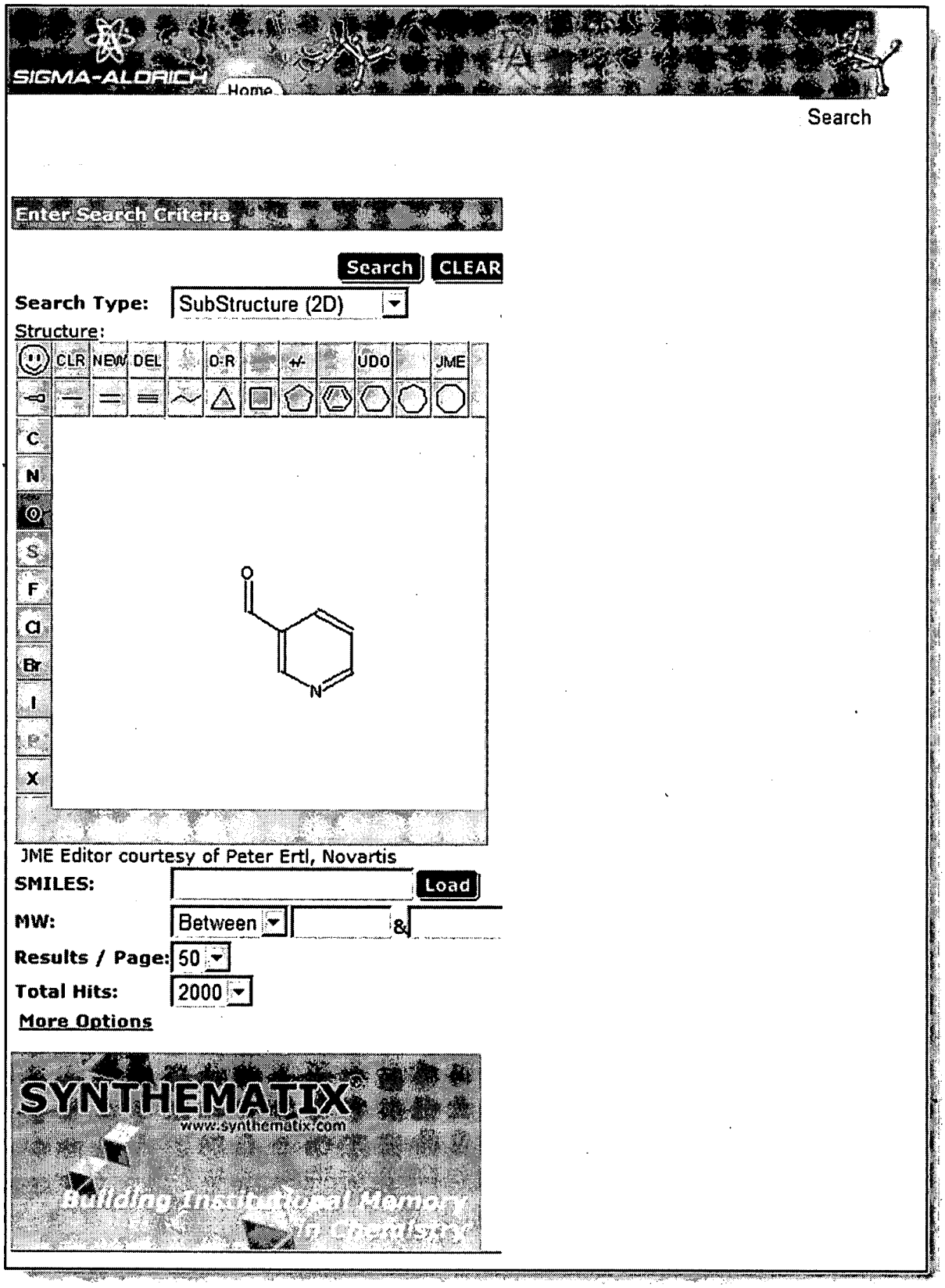
169 USPQ at 367 paragraph 3. **(F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:** The examiner will first discuss the limitations inherent to the paucity of available starting materials, as well as the inherent limitations of the chemistry used to prepare the examples, followed by a detailed analysis of substituents that may have the claimed utility. As per MPEP:

As per MPEP:

> A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in In re Ghiron, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. In re Howarth, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

The applicant is relying upon a three component coupling reaction between an aldehyde, malononitrile, and a 4-hydroxy indole. A great many phenyl aldehydes are commercially available, but the number is finite, however the examiner is most disturbed and will take issue with the paucity of commercial heteroaryl aldehydes (3-pyridyl, 2-thienyl, 3-indolyl, 2-pyrazinyl, and 2-quinoxalinyl). The protracted list for R10-R14, R15-R18 or what is sometimes referred to as an "optional substituent" is not enabled. The

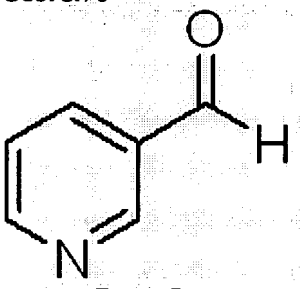
examiner has done a search for the 3-pyridyl aldehydes in the Sigma-Aldrich Catalog (St Louis, MO)


SIGMA-ALDRICH
Home
Search
Enter Search Criteria
Search
CLEAR
Search Type:
SubStructure (2D)
Structure:
CLR
NEW
DEL
O-R
UDO
JME
C
N
O
S
F
Cl
Br
I
P
X
O
N
JME Editor courtesy of Peter Ertl, Novartis
SMILES:
Load
MW:
Between
&
Results / Page:
50
Total Hits:
2000
More Options
SYNTHEMATIX
www.synthematix.com

Only 12 such aldehydes are available commercially.

Name: 3-Pyridinecarboxaldehyde
IUPAC: nicotinaldehyde
MF: C_6H_5NO
CAS #: 500-22-1
MW: 107.11
MDL #: MFCD00006382
BP: 78 - 81 °C
FP: 140
d: 1.1410

Score:76

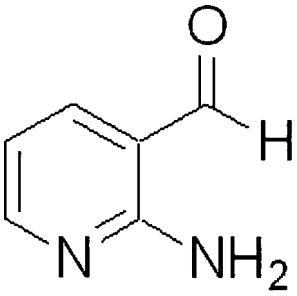


Zoom In

82720 purum, ≥97.0% (GC)
P62208 98%

Name: 2-Amino-3-pyridinecarboxaldehyde
IUPAC: 2-aminonicotinaldehyde
MF: $C_6H_6N_2O$
CAS #: 7521-41-7
MW: 122.12
MDL #: MFCD01830382

Score:59

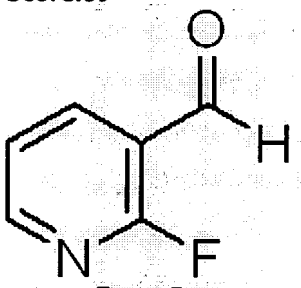


Zoom In

639109 97%

Name: 2-Fluoro-3-pyridinecarboxaldehyde
IUPAC: 2-fluoronicotinaldehyde
MF: C_6H_4FNO
CAS #: 36404-90-7
MW: 125.10
MDL #: MFCD03095270
BP: 50 °C
FP: 164
d: 1.25

Score:59

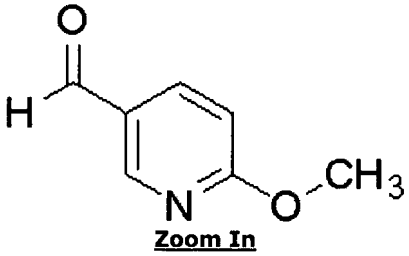


Zoom In

664111 97%

Name: 6-Methoxy-3-pyridinecarboxaldehyde
IUPAC: 6-methoxynicotinaldehyde
MF: $C_7H_7NO_2$
CAS #: 65873-72-5
MW: 137.14
MDL #: MFCD02683446
FP: 225

Score:57



Zoom In

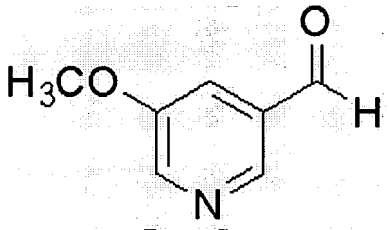
533068 98%

Name: 5-Methoxy-3-pyridinecarboxaldehyde
IUPAC: 5-methoxynicotinaldehyde
MF: $C_7H_7NO_2$
CAS #: 113118-83-5
MW: 137.14
MDL #: MFCD07437946

Score:50

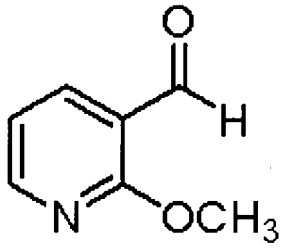
676489 96%

FP: 212



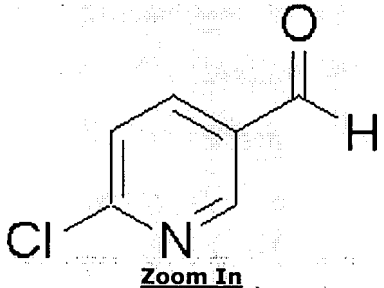
Zoom In

Name: 2-Methoxy-3-pyridinecarboxaldehyde **Score:**51 632139 96%
IUPAC: 2-methoxynicotinaldehyde
MF: $C_7H_7NO_2$
CAS #: 71255-09-9
MW: 137.14
MDL #: MFCD04115112
BP: 200 - 201 °C
FP: 205
d: 1.1610



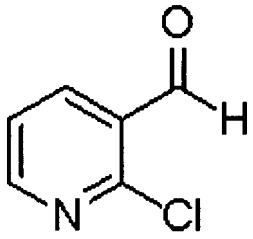
Zoom In

Name: 6-Chloropyridine-3-carboxaldehyde **Score:**55 596175 97%
IUPAC: 6-chloronicotinaldehyde
MF: C_6H_4ClNO
CAS #: 23100-12-1
MW: 141.55
MDL #: MFCD03095223



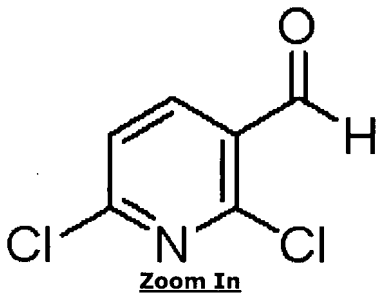
Zoom In

Name: 2-Chloro-3-pyridinecarboxaldehyde **Score:**56 632155 97%
IUPAC: 2-chloronicotinaldehyde
MF: C_6H_4ClNO
CAS #: 36404-88-3
MW: 141.55
MDL #: MFCD01315308
FP: 230



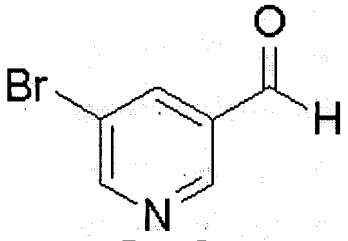
Zoom In

Name: 2,6-Dichloropyridine-3-carboxaldehyde **Score:**51 651958
IUPAC: 2,6-dichloronicotinaldehyde
MF: $C_6H_3Cl_2NO$
CAS #: 55304-73-9
MW: 176.00
MDL #: MFCD07369746



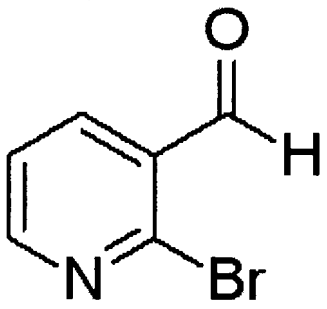
Zoom In

Name: 5-Bromo-3-pyridinecarboxaldehyde **Score:**57 644102 97%
IUPAC: 5-bromonicotinaldehyde
MF: C_6H_4BrNO
CAS #: 113118-81-3
MW: 186.01
MDL #: MFCD03265758



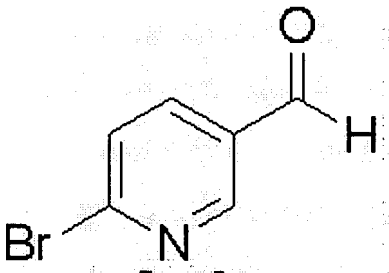
Zoom In

Name: 2-Bromo-3-pyridinecarboxaldehyde **Score:**57 632147 96%
IUPAC: 2-bromonicotinaldehyde
MF: C_6H_4BrNO
CAS #: 128071-75-0
MW: 186.01
MDL #: MFCD04966945



Zoom In

Name: 6-Bromo-3-pyridinecarboxaldehyde **Score:**56 596280 95%
IUPAC: 6-bromonicotinaldehyde
MF: C_6H_4BrNO
CAS #: 149806-06-4
MW: 186.01
MDL #: MFCD04115419



Zoom In

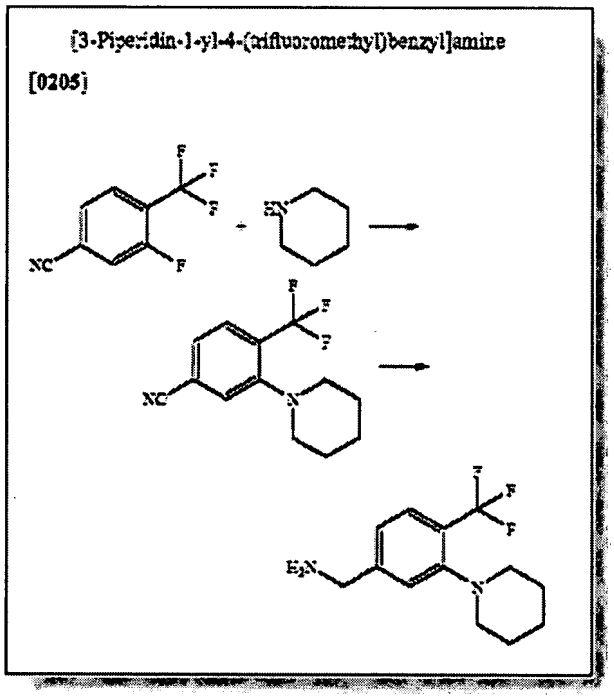
Not only does this cast serious doubt on the operability of the scope of the invention, it also points to a severe deficit in the disclosure, where individual compounds are claimed yet we are given no guidance as to how the aldehydes may be prepared. For example where are directions for the preparation or commercial availability of 5-chloro-

6-hydroxy-3-pyridine-3-carboxaldehyde or 5-bromo-6-acetoxypyridine-3-carboxaldehyde? According to the U.S. Court of Customs and Patent Appeals in *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 101, "[o]rdinarily no problem in this regard arises since the method of preparing almost all starting materials can be set forth in writing if the materials are not already known and available to the workers in the art, and when this is done the specification is enabling to the public". *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 104, "it is essential that there be no question that, *at the time an application for patent is filed,* (emphasis in original) the invention claimed therein is fully capable of being reduced to practice (i.e., that no technological problems, the resolution of which would require more than ordinary skill and reasonable time, remain in order to obtain an operative, useful embodiment)." That is not the situation here. Rather we find very little direction as to how the many required staring aldehydes are to be obtained. Where may the directions to prepare or buy them be found?

In re Howarth, 210 USPQ 689, (claimed derivatives of clavulanic acid not enabled by specification lacking information of how prepare the clavulanic acid or directions to reference materials containing such information), *Ex parte Schwarze* 151 USPQ 426 (where starting material is not known to art as of date of filing application, there must be included a description of preparation thereof to enable one skilled in this art to carry out applicant's invention), *Ex parte Moersch* 104 USPQ 122 (claims to process for the production of (1)-y1-p-nitrophenyl-2-dichloracetamindo-propane-1,3-diol not enabled because of failure to describe source or method of obtaining starting

compound; although starting compound is identified by means of appropriate name and by structural formula).

While the inability of the chemist to make compounds that he cannot obtain starting materials is indeed undue experimentation. There is serious reason to doubt the functioning of the scope claimed in applicant's synthesis. For example, piperdine is a base and is the catalyst for applicant's ternary condensation reaction, however piperidine is a good nucelophile and when the extremely electron deficient aldehydes of the instant case are employed it would not be unexpected to see Nucleophilic Aromatic Substitution occur (SN_{Ar}). Indeed numerous examples of this very same reaction are found in the literature see for example Tajimi et. al. US 20060135505 pg.15 reproduced below:



In fact the operability of aldehydes like the one required for the synthesis of 40F is remarkable. One would certainly not expect trifluoromethyl or nitro substituted fluoroaldehydes to react in the desired manner.

While these are clear limitations of the chemistry involved in preparing the compounds, several things become very clear, upon close examination of applicant's data: 1) The substituent R1 can have a marked impact on the activity (asserted utility) of the compounds. For example compounds bearing alkylamino (Example 6) and oxiranyl (Example 19) side chains, show markedly reduced activity compare to (4, 5,16, 17, 38, 40F). 2) Analogs with 2 substitution were not made or tested, however upon looking to the literature it is clear that these are not compounds that function well in applicants desired manner in compounds that differ only in the presence or absence of a ring-fusion by a methylene or methane carbon (away from the site at issue), as stated by (Kemnitzer, W. et. al. Journal of Medicinal Chemistry 2004,47, 6299-6310, cited by applicant NPL27) on pg. 6302 column 1-2

> "Compounds **1h** and **1i**, with a methoxy group at the 2-position, are >40-fold less active than the 3,4,5-trimethoxy analogue **1b**, suggesting that there might be a space-limited
>
> pocket around the 2-position, or due to steric effect, the 2-methoxy group forces the phenyl ring into an unfavorable position. Compound **1j** was >130-fold less active than **1c**, confirming that substitution in the 2-position, is not preferred.....The 3,4-dimethoxy analogue **2d** was

>10-fold less potent than **2a**, further supporting the notion that substitution in the 3,5-position is important for activity and substitution in the 4-position contributes little to potency. Similar to what has been observed in the trisubstituted analogues, the 2,3-dimethoxy analogue **2e** was >44-fold less active than **2a**, further confirming that substitution in the 2-position is not preferred."

3) The identity of the group in the 4- position is critical for activity, Kemnitzer at pg. 6303, "The nonaromatic cyclohexyl analogue (5a) was >2.5- fold less active than 3l, suggesting that a planar structure of either a phenyl or pyridyl group is preferred in the 4-position of the chromene structure. Extending the nonsubstituted phenyl ring from the 4-position via an ethyl linker (5b) resulted in >3.5-fold reduction in potency relative to 3l, **suggesting that the binding pocket in the 4-position of chromene is size limited.....confirming that there is a size-limited pocket in the 4-position of chromene.**" It is very clear that the long list of groups recited in the claims of the applicant: "RI0-R14 are independently hydrogen, halo, haloalkyl, aryl, fused aryl, carbocyclic, a heterocyclic group, a heteroaryl group, Cl-~0 alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, methylenedioxy, ethylenedioxy, carbonylamido or alkylthiol; or R10 and RII, or RII and RI2, taken together with the atoms to which they are attached form an aryl, heteroaryl, partially saturated carbocyclic, saturated carbocyclic, partially saturated heterocyclic or saturated

heterocyclic group wherein said group is optionally substituted." will simply not posses the desired activity due to this size restriction. Moreover, certain benzopyrans are carcinogens (Radwan et. al. Phosphorous, Sulfur, and Silicon 1995, 101, 207-211, sentence 2, cited by applicant). The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a):

"A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification , at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has few working examples in this unpredictable art without undue experimentation.

Genetech Inc Vs Nova Nordisk 42 USPQ 2d 1001 "A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell, Ph.D. whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

CECILIA TSANG
SUPERVISORY PATENT EXAMINER